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(19) (CA) # CANADIAN PATENT

(54) PHENOXY-ALKYL-CARBOXYLIC ACID DERIVATIVES AND THE PREPARATION THEREOF

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The invention concerns new derivatives of phenoxy-alkyl-carboxylic acids and their method of preparation, characterised in that para-hydroxy-benzaldehyde, a para-hydroxy-phenone, or p-hydroxy-benzoic acid is condensed with chloro-acetic acid or one of the superior homologues thereof, the acid or the diacid obtained being possibly converted afterwards.

The acid obtained can be converted into an ester according to the classic sulphuric esterification method in the presence of a chosen alcohol.

The ester obtained can be also converted into an amide by boiling to reflux in the presence of chosen aromatic or aliphatic amide or its derivatives.

The amide can also be obtained by means of an acid chloride according to the usual methods, from the corresponding acid.

The aldehyde or cetone function is converted into an axime by heat treatment in the presence of hydroxylamine chlorohydrate.

The acid obtained is possibly converted into its halogenated para-ω derivative by the addition of a halogen to a solution of the said acid in acetic acid in the presence of acetic anhydride.

The para-ω halogen derivatives of the acid can also be converted into an ester, amide or oxime.

The ester or oxime can also be converted into phenoxy-alkyl, carbohydroxamic acid by bringing them to reflux in ethyl alcohol containing hydroxylamine and sodium.

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The dehydration of the para-formyl-oxime-phenoxy-alkyl carboxylic acid esters by boiling to reflux in the presence of acetic anhydride gives new chemical bodies as the esters of para-cyano-phenoxy-alkyl-carboxylic acids. The corresponding amides are obtained by boiling the said esters in the chosen amine.

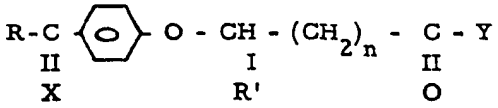
The esters of para-cyano-phenoxy-alkyl-carboxylic acids are converted into para-carboxamide-phenoxy-alkyl-carboxylic acids by oxygenated water in a warm medium of alcalin. These acids can be, in their turn, esterified then converted into an amide.

According to another characteristic of the invention the para-carboxy-phenoxy-alkyl-carboxylic acids diacids obtained according to the general process can then possibly be submitted to an esterification or an amidification or can be converted into a corresponding hydroxamic acid.

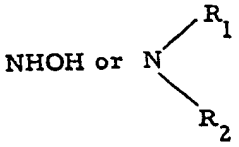
The new compounds obtained by these processes are particularly remarkable for their therapeutic applications in neutotrope, anti-inflammation, normo-lipemiant medicines, for example.

The formulae of the chemical compounds according to the invention are characterised by the presence on a phenyl ring of a cetone aldehyde group, convertable into an oxime, acid, ester, amide, hydroxamic or nitrile acid in para position in relation to the oxy-alkyl group, or by the presence of a halogen in ω position of the chain in para position in relation to the oxy-alkyl group, and by the presence of an oxy-alkyl chain of 2, 3 or 4 carbon atoms supporting an acid, ester, amide, or carbohydroxamic function.

The derivatives according to the invention comply to the general formula :

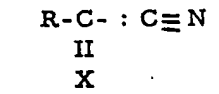


where R is -H or NH_2, $-CH_3$; $-CH_2-CH_3$; $-CH_2-CH_3$; $-C_6H_5$ or the halogen derivatives of the preceding groups, -OH; $-OCH_3$; OC_2H_5;



(where R_1 and R_2 can be linear radicals such as $-CH_3$ or $-CH_2CH_3$ or a cycle such as piperidine, methyl 2 piperidine, piperazine, morpholine, pyrrolidine, methyl 4 piperidine N-phenyl piperazine, N-p methoxy-phenyl-piperazine, N-methyl 4 piperazine, N-p chlorophenyl piperazine or hexamethylemimine or ethylamino ethylamine).

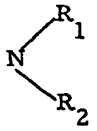
X is = O or = N-O-H



R' is -H, or $-C_6H_5$

n = o, 1, 2 or 3 normo or iso for R' = H

n = 1, 2 or 3 for R' = C_6H_5

Y is - OH; $-OCH_3$; $-OC_2H_5$, or 

(where R_1 and R_2 can be radical linears such as CH_3 or CH_2CH_3 or represented by a cycle such as piperidine methyl 2 piperidine, piperazine, morpholine, pyrrolidine, methyl 4 piperidine, N-phenyl piperazine, N-p methoxy-phenyl piperazine, N-methyl 4 piperazine, N-p chlorophenyl piperazine or hexamethylemimine, or ethyl amino ethyl amine.)

The invention will be better understood by referring to the following description detailing the preparation of some of the new

chemical compounds by way of example.

A : Synthesis of p-ceto-alkyl-carboxylic or p-formyl-alkyl-carboxylic acids and their derivatives.

I - Synthesis of acids

0, 6 mole of Na OH

0, 3 mole of p-hydroxy-benzaldehyde or of p-hydroxy-acetophenone or of its superior homologues propiophenone and butyphenone.

0, 3 mole of chloroacetic, chloropropionic or chloro-butyric-acids are introduced into a balloon-flask containing 600 ml. of water.

The solution is brought to reflux boiling for 8 hours. After cooling it is acidified with pH3, by 12N HCl. The acid precipitates and is filtered. The product obtained is redissolved in ether and extracted by an acidified aqueous solution. The acid is recrystallised in water by cooling to the ambient temperature.

The average yield of this operation is in the order of 65%.

By this method of synthesis five types of products deriving from para-formyl-phenoxy-alkyl-carboxylic acid, from para acetyl-phenoxy-alkylcarboxylic acid, from para propionyl-phenoxy-alkyl-carboxylic acid, from para-butyryl-phenoxy-alkylcarboxylic acid and from para-benzoyl-phenoxy-alkyl- carboxylic acid can be obtained.

The alkyl derivatives corresponding to each of the five series can be an acetic propionic chain (normo or iso).

In order to obtain the homologues of these five series for which the alkyl link is an iso-butyric link, a slightly different method must be employed, which consists of : in a three-column balloon flask of

1,000 cm^3, provided with mechanical stirer and a reflux refrigerant surmounted by a $CaCl_2$ column is introduced 0,1 mole of para-hydroxyphenylcetone dissolved in 100 ml of anhydrous acetone.

Under agitation 0,5 mole of Na OH in pulverised pastiles is added. It is brought up to reflux by heating in a water bath maintaining the agitation. Sodium phenate precipitates after about 15 to 20 minutes.

10 ml of anhydrous $CHCl_3$, diluted in 20 ml of anhydrous acetone is introduced by a bromine flask.

Reflux heating is then continued for four hours.

300 ml of water is then added and the evaporation of the acetone is obtained in a vacuum. The aqueous solution is then acidified to pH3 with 12N HCl then extracted twice over by 200 ml of ether.

The etheral solution is extracted in two successive timesby 150 ml of saturated solution of sodium carbonate acid.

By acidification of the carbonated solutions to pH3 by 12N HCl an oil is formed which is extracted by 400 ml of ether. The etheral solution is poured off, dried by Na_2SO4, then evaporated in a vacuum.

The phenoxy-isobutytric acid takes the form of a mass. It is recrystallised in a mixture of alcohol and water.

Then phenoxy-isobutyric acids obtained according to this method are synthesised with a yield of 50%.

By way of example, the following products exhibit the following particular properties :

a) Para-butyryl-phenoxy-isobutyric acid

Fusion point : 88°C

Soluble in ether, alcohol and acetone

Insoluble in water

b) Para-benzoyl phenoxy-isobutyric acid :

Fusion point 130°C

Soluble in ether, alcohol and acetone

Insoluble in water

II - Esterification

10 g of an acid obtained in I are dissolved in 150 ml of methanol, ethanol or propanol.

150 ml of anhydrous benzine

1 ml of 36N H_2SO_4 are gradually added to a flask. After boiling to reflux for two hours, the azeotrope benzine-alcohol is distilled until all the benzine is eliminated.

The alcoholic solution is next concentrated in a vacuum. The oil obtained is recovered by 200 ml ethyl ether, the solution is washed in water then dried on Na_2SO_4. After concentration of the etheral solution in a vacuum the ester is obtained in the form of a yellow oil or in crystallised form according to the case.

Examples

a) The ethylic ester of the p -acetyl-phenoxy-iso butyric acid is obtained after dissolving the acid in absolute ethanol, the addition of benzine and H_2SO_4, boiling to reflux then purificiation; it is a liquid soluble in alcohol, ether and chloroform, and in water; its boiling point is 120°C at 0,03 mm Hg. The yield of the preparation is in the neighbourghood of 85%.

b) The ethyl esters of para butyl phenoxy iso butyric acid is obtained in the same conditions from p butyl-phenoxy-aceti-acid, with a yield of 70%. It is a liquid soluble in alcohol and ether,

insoluble in water and its boiling point is 144°C at 0,05 mm Hg.

III - Amidification

1) From esters

8 g of an ester is obtained and dissolved in about 25 ml of an amine previously dried on potash. The solution is refluxed for 3 hours. The amine generally crystallises by simple cooling or by the addition of a slight quantity of water. The complete precipitation is obtained by the slow addition of 200 to 300 ml of water. Purification is carried out by recrystallation in a mixture of alcohol and water.

2) From acid chlorates

It is possible to treat the acid chlorates obtained according to the usual methods, in the same conditions as that above in III 1) in the presence of amine in order to obtain the required amide.

The following are given by way of example :

a) Morpholine amide of p-formyl phenoxy acetic acid is obtained according to 1 or 2 above. The yield is 65% and the product is soluble in alcohol and insoluble in water; the fusion point for the amide is 116°C.

b) The amide of p chloro-phenyl 4 piperazine and of the p formyl phenoxyacetic acid is obtained by methods described in 2 above, with a yield of 45%; its fusion point is 120°C.

c) The amide of p chlorophenyl 4 piperazine and of p acetyl phenoxy acetic acid is obtained according to 1 above with a yield of about 40%. Its fusion point is 115°C; it is soluble in alcohol, slightly soluble in ether, and insoluble in water petroleum ether and hexane.

d) p (acetyl-phenoxy acetyl) 1 morpholine is obtained according to 1 above. It is soluble in alcohol, insoluble in water, and

petroleum ether. Its fusion point is 112°C, with a yield of 60%.

e) (p acetyl phenoxy acetyl) 1-methyl 4 piperidine is obtained according to 1 above with a yield in the order of 40% its fusion point is 60°C; it is soluble in alcohol and ether, insoluble in water and petroleum ether.

f) (p acetyl phenoxy acetyl) 1-hexamethylemimine is obtained according to 1 above with a yield of 50%; it is soluble in alcohol and ether insoluble in water. Its fusion point is 78°C.

g) N (p acetyl phenoxy acetyl) diethyl amino ethyl amine is obtained according to 1 above, with a yield of 35%. It is insoluble in water and petroleum ether, soluble in alcohol and ether, and its fusion point is 75°C.

h) Piperidine amide p formyl phenoxy acetic acid is obtained by the treatment indicated above in 1 or 2. A crystallised product is obtained of which the fusion point if 96°C, it is soluble in ether, alcohol and most organic solvants and insoluble in petroleum ether and water. The yield of the preparation is about 60%.

i) Piperidine amide of p acetyl phenoxy acetic acid is obtained in the conditions described in 1 above. A crystallised product is obtained the fusion point of which is 97°C with a yield of about 60%. This product is soluble in alcohol and most organic solvents, but insoluble in water and petroleum ether.

The amides complying to the general formula for which, $R' = C_6H_5$ are also obtained by applying the processes 1 and 2 above.

IV - Production of oximes

0,1 mole of an amide obtained as in III is made into a solution with 500 ml of absolute ethanol. 7g hydroxylamine and chlorhy-

drate and 5, 8 g of soda are added to the solution which is then refluxed for three hours. After the addition of 100 ml of water, the oxime precipitates in the hydro-alcoholic solution, by concentration in a vacuum. After filtration, the oxime is purified by recrystallisation in a mixture of alcohol and water.

Examples:

a) The oxime of the piperidine amide of p formyl phenoxy-acetic acid is obtained in the above conditions. The crystallised oxime is obtained with a yield of about 70% : its fusion point is 135°C. It is soluble in alcohol but insoluble in water.

b) (p formyl oxime phenoxy acetyl) 1 morpholine is obtained in the above conditions. It is soluble in alcohol, insoluble in water, its fusion point is 169°C and the yield is 60%.

c) p acetyloxime of the phenoxy acetic acid is obtained in the previous conditions for this variant after the PH alkalin obtained by the piperidine used in equimolecular proportions with the chlorhydrate of hydroxylamine. The product is obtained with a yield of 55%. It is soluble in alcohol and bicarbonated water, insoluble in water.

d) p ecetyl oxime of phenoxy ethyl acetate is obtained in the same conditions as for (b) from the p acetyl phenoxy acetic ester with a yield of 65% It is soluble in alcohol, insoluble in water. Its fusion point is 103°C.

e) p acetyl oxime of the phenoxy-acetyl amido piperidine is obtained by condensation of the corresponding amide with chlorhydrate of hydroxylamine in alcohol in the presence of soda, boiling to reflux, then purification. The yield is 70%. The product is soluble in alcohol and insoluble in water; its fusion point is 168°C.

f) (p acetyl oxime phenoxy acetyl) 1 morpholine is obtained according to the same process with a yield of 70%. The product is soluble in alcohol, insoluble in water. Its fusion point is 145°C.

g) (p acetyl oxime phenoxy acetyl) 1 methyl 4 piperidine is obtained with a yield of 60%. The product is soluble in alcohol, insoluble in water; its fusion point is 166°C.

h) (p acetyl oxime phenoxy acetyl) 1 chlorophenyl 4 piperazine is obtained with a yield of 60%. The product is soluble in alcohol, very slightly soluble in ether, insoluble in water. Its fusion point is 194°C.

i) (p acetyl oxime phenoxy acetyl) 1 hexamethylemimine is obtained with a yield of 60%. It is soluble in alcohol, insoluble in water. Its fusion point is 134°C.

j) N (p acetyl oxime phenoxy acetyl) diethyl amino ethyl amine is obtained in the above conditions with a yield of about 50%. It is soluble in alcohol, insoluble in water; its fusion point is 130°C.

The oximes derived from compounds complying with the general formula for which $R' = C_6H_5$ are also obtained according to the above process.

V - ω Halogen derivatives

Another process according to the invention consists of the conversion of the phenoxy alkyl carboxylic acids into their ω halogen derivatives, the formula for which remains consistent with the general formula but for which R signifies $ACH_2-(CH_2)_n$, A representing a halogen in n' = 0, 1, 2, 3 normo or iso positions.

The fixing of the halogen on the chain, bromine for example, is obtained by the action of the bromine on phenoxy alkyl

carboxylic acid diluted in acetic acid. The bromine is added to the solution drop by drop in the presence of acetic anhydride, the precipitate obtained being washed and recrystallised after being dissolved in boiling water.

Such halogenous ω acids complying to the general formula can be converted into their esters, amides, and oximes by application of the methods described in II, III and IV.

Examples :

1 - p ω bromo acetyl phenoxy acetic acid is obtained by bromination as described above.

The product is obtained with a yield of about 70%. Its fusion point is 183°C. It is soluble in alcohol and in warm water, insoluble in cold water.

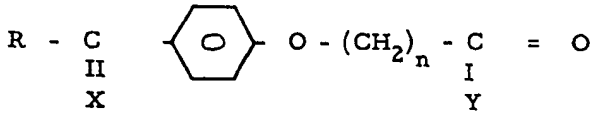
2 - p ω bromo phenoxy ethyl acetate is obtained by esterification of the preceding acid conforming to the conditions described in II with a yield of about 90%. The product is soluble in alcohol, benzine and insoluble in water. Its fusion point is 80°C.

3 - (p ω bromo acetyl phenoxy acetyl) 1 -piperidine is obtained by condensation of the previous ester and of the piperidine in the conditions described in III (1) = with a yield of about 50%. The product is soluble in warm alcohol, insoluble in water, and its fusion point is 96°C.

4 - (p ω bromo acetyl oxime phenoxy acetyl) 1 piperidine is obtained by condensation of the previous product with hydroxylamine in the presence of soda, with a yield in the order of 40%. It is soluble in the usual solvents, its point of fusion is 220°C.

VI - Phenoxy alkyl carbohydroxamic acids and their derivatives

Phenoxy alkyl carboxylic acids and their derivatives of the general formula :



can be converted in order to obtain the phenoxy alkyl carbohydroxamic acids and their derivatives where Y is NHOH.

The general method consists of dissolving the corresponding esters or their p alkyl oxime derivatives in ethyl alcohol containing hydroxylamine and sodium, to be brought to reflux, then to precipitate the acid bringing the solution obtained having previously had the alcohol removed in an acid medium.

Examples :

a) p formyl-oxime phenoxy-aceto hydroxamic acid is obtained by dissolving in 500 ml of alcohol :

2-atom grams of sodium, 1 mole of hydroxylamine chlorhydrate, and 1 mole of p formyl oxime phenoxy ethyl acetate obtained according to (IV) or 3 atom grams of sodium, 2 moles of hydroxylamine chlorhydrate and of p formyl phenoxy ethyl acetate obtained according to (II).

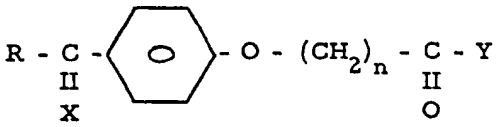
After coiling to reflux the NaCl formed is eliminated by filtration : 200 ml of water is added and the alcohol evaporated in a vacuum. The aqueous solution is acidified to pH3. The precipitate obtained is filtered and recrystallised in alcohol.

The product is obtained with a yield of about 50%. It is soluble in alcohol, insoluble in water, its fusion point is 198°C.

b) p acetyl oxime phenoxy aceto hydroxamic acid is obtained according to the previous procedure from the oxime phenoxy acetate of ethyl or the p acetyl phenoxy ethyl acetate with a yield of 55%.

VII - Para cyano alkyl carboxylic acids

Another process according to the invention consists of transforming the p formyl phenoxy alkyl carboxylic acids of such type that their general formulae would be :



with X representing N-OH R representing NH_2

or R - C(=X) : $C \equiv N$

The process consists of dehydrating the esters of p formyl oxime phenoxy alkyl carboxylic acids by acetic anhydride during boiling to reflux. The esters of cyano phenoxy alkyl carboxylic acids are thus obtained. The corresponding amides can be obtained by boiling to reflux the preceding body dissolved in the corresponding amine or by dehydration of the (p-formyl-oxime-phenoxy-alkyl) 1 amido by acetic anhydride.

The p cyano phenoxy alkyl carboxylic acids can be converted into p carboxamide phenoxy alkyl carboxylic acids by oxygenated water in a warm alkaline medium. These acids can be esterified then converted into amides according to the methods described in II and III.

The (p carboxamide oxime phenoxy alkyl) 1 amidos are obtained directly from the p-carboxamide phenoxy alkyl carboxylic acids, by amidification according to III.

Examples :

a) p cyano phenoxy ethyl acetate is obtained by the following successive operations :

- Conversion of the p formyl phenoxy ethyl acetate into its oxime by condensation of hydroxylamine chlorhydrate in the presence of pyridine anhyde in equimolecular proportions by boiling to reflux.

- After recrystallisation of the previous body, 15 g of this are brought to reflux in 100 ml. of acetic anhydride. It is next hydrolized by 100 ml of warm water; after cooling, it is alkalinized by 100 g of sodium bicarbonate and the p-cyano derivative is precipitated and recrystallised in the minimum of alcohol.

Thus, 9.5 g of the product are obtained, its fusion point being 57°C.

b) the p carboxamide phenoxy acetic acid is obtained by the action of 15 ml of H_2O_2 110 volumes on 8 g of the previous bodies warmed in 100 ml of water containing 3 g of potash. After cooling, the acid is precipitated by the addition of 12N HCl up to PH3. 7 g of acid are obtained; its fusion point is 250°C.

c) p-carboxamide phenoxy ethyl acetate is obtained by boiling to reflux 8 g of the previous acid in 100 ml of absolute alcohol and 100 ml of benzene. After distillation of the azeotrope it is concentrated in a vacuum, the ester precipitates and it is next recrystallised in the minimum of alcohol to 95%. 5g of ester are obtained; its fusion point is 143°C.

d) (p carboxamide phenoxy acetyl) 1 piperidine is obtained from the preceding ester according to the method described in III (1) with a yield in the order of 55%. Its fusion point is 168°C.

e) (p cyano phenoxy acetyl) 1 piperidine is obtained either by dehydration from (p formyl oxime phenoxy acetyl) 1 piperidine by warm acetic anhydride or by treatment with p cyano phenoxy ethyl acetate according to the process described in III (1). The yield is 90%

The product has a fusion point of 112°C. It is soluble in alcohol and in ether, insoluble in water.

f) (p carboxamide oxime phenoxy acetyl) 1 piperidine is obtained by the process described in IV from the previous amide with a yield of 40%. Its fusion point is 180°C. It is soluble in water, soluble in alcohol.

B- Synthethis of p carboxy phenoxy alkyl carboxylic acids and their derivatives

I - Synthesis of the acids

The p carboxy phenoxy alkyl carboxylic acids are obtained in the following manner :

- 3 moles of pellets of soda, 1 mole of p hydroxy benzoic acid and 1 mole of chloro-acid are brought to reflux in 1.3 litres of water then immediately acidified to PH3. The di-acid precipitates, is isolated by filtration, washed in water then alcohol, and the product has a yield of about 80%.

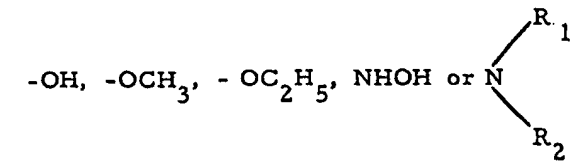
Examples :

p carboxy phenoxy acetic acid is obtained by boiling to reflux with 120 g of soda, 138 g p hydroxy benzoic acid and 95g of chloroacetic acid in 1.3 litres of water, then acidification to PH3. After purification, 159 g of powder are obtained, its fusion point being 282°C.

II - Synthesis of ester, amide, and carbohydroxamic derivatives

It is possible to convert the series of p carboxyphenoxy alkyl carboxylic acids into their ester, amide and carbohydroxamic derivatives according to the methods described above in AII, III, and VI. The compounds obtained conform to the general formula in such

a way that R can be



$-OH$, $-OCH_3$, $-OC_2H_5$, NHOH or $N(R_1)(R_2)$

R_1 and R_2 can be linear radicals such as CH_3 or CH_2 CH_3 or represent a ring such as that of piperidine, methyl 2 piperidine, piperazine, morpholine, pyrrolidine methyl 4 piperidine, N-phenyl piperazine, N-p methoxy phenyl piperazine N-methyl 4 piperazine, N-p chlorophenyl piperazine, hexamethylemimine or ethylamino ethylamine.

Y can also be -NHOH as indicated above in A VI

1) Esterification

The di-acids obtained can be esterified according to the general method described in A II. The carboxyl in para position can also be esterified by maintaining the di-acid in suspension in the chosen alcohol at reflux under a current of HCl.

Examples :

a) p carboxy phenoxy ethyl acetate is obtained by boiling to reflux the previous body in a sulphuric medium in a mixture of ethyl alcohol and benzene. After distillation of the excess ethyl alcohol and solvent, the ester is isolated and recrystallised in benzene. The product is obtained with a yield of about 60%; its fusion point is 138°C; it is soluble in alcohol and in bicarbonated water, and insoluble in water.

b) The ethylic di-ester of p carboxy phenoxy acetic acid is obtained by boiling to reflux a saturated solution of HCl containing 75 g of di-acid in 500 ml of ethyl alcohol under constant bubbling with HCl. The di-acid dissolves slowly, reflux and the current of HCl being continued 2 to 4 hours after completion of the dissolving.

The solution is discoloured or black, then evaporated in a vacuum, the oil obtained put into a solution with ether and washed in water, then with water saturated with sodium bicarbonate; after evaporation of the solvents the oil is distilled in a vacuum, its boiling point is 125°C at 05 mm Hg. The ester forms into a mass; 50 g of product is obtained and its fusion point is 32°C. It is soluble in alcohol and in ether, insoluble in water.

2 - Amidification

Amidification is obtained according to the general method described in A III.

Examples :

a) (p carboxy phenoxy acetyl) 1 piperidine is obtained according to the method described in A III (1), from the ester described above in B II (1a) with a yield of about 45%. Its fusion point is 190°C; it is soluble in alcohol and in bicarbonated water, insoluble in water.

b) (p methyl oxy varbonyl phenoxy acetyl) 1 piperindine is obtained from the methyl di-ester of carboxy phenoxy acetic acid, this being obtained according to the method described in BII (1). Amidification is carried out according to the general method described in A III; the yield i s in the order of 74%. The product has a fusion point of 104°C. It is soluble in alcohol and ether, insoluble in water and petroleum ether.

c) (p acetyl oxy carboxyl phenoxy acetly) 1 piperidine is obtained from the ethylic di-ester described above in B II (1b) with a yield of the order of 70%, and having a fusion point of 61°C. It is soluble in alcohol and ether, insoluble in water and petroleum ether.

d) (p carboxy phenoxy acetyl) 1 morpholine is obtained according to the general method of amidification from the ester obtained as above in B II (1a), with a yield of 55%. It is soluble in alcohol and bicarbonated water, insoluble in water; its fusion point is 183°C.

e) (p piperidino oxo) phenoxy ethyl acetate is obtained from the ester described in B II (1a). Previously chlorinated into p by the action of PCl 5 is equimolecular proportions under heat. The chloride of the acid obtained is made into a benzene solution, and a solution of piperidine in benzene is added to the ice bath in the proportions of 1 : 2. The amide is separated by concentration in a vacuum, and recrystallisation. It is obtained with a yield of 40%. Its fusion point is 90°C. It is soluble in alcohol and in ether, insoluble in water.

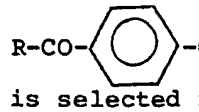
f) p carboxamide phenoxy acetamide is obtained from carboxy phenoxy acetic acid, previously converted into its dichloracid derivative, this being put in the presence of NH4 OH. The diamide precipitates; after purification the yield is 70%. Its fusion point is 265°C and it is insoluble in the usual solvents.

3). Hydroxamic acids

The corresponding hydroxamic acids are obtained according to the general method described in A VI

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. Process for preparing compounds having useful pharmaceutical properties of formula



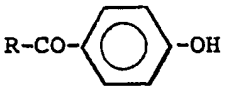
(I) wherein

A is selected from the group consisting of $C(CH_3)_2$ and a phenyl substituted alkyl chain having from 1 to 4 C;

R is selected from H, free or W-halogenated CH_3, C_2H_5 and C_3H_7 groups and C_6H_5; and

Y is selected from OH, lower alkoxy having 1 to 3 C, aliphatic amines selected from the group consisting of dimethyl-, diethyl-, ethylamino-ethylamine, and heterocyclic amines selected from the group consisting of piperidine, 2-methyl piperidine, 4-methyl piperidine, morpholine, pyrrolidine, piperazine, N-phenyl-, N-methyl, N-p-methoxyphenyl-, N-p-chlorophenyl-piperazine and hexamethyleneimime,

which comprises reacting a compound of formula



(II) with a compound of formula

Cl-A-COY (III)

in the presence of a basic condensing agent, the compound (III) being selectively generated in situ when A is $C(CH_3)_2$ from anhydrous $CHCl_3$ and acetone, and compound (I) being optionally eventually converted into the corresponding oxime.

2. A process according to claim 1, wherein Y is OH, which comprises esterifying the acid by means of a lower alkanol YOH.

B 3. A process according to claim 1, wherein Y is a lower alkoxy, which comprises ~~reaching~~ reacting the ~~ster~~ ester with a secondary or heterocyclic amine HY to convert the ester into an amide.

4. A process according to claim 1, wherein compounds (I) are converted into oximes by means of hydroxylamine hydrochloride.

5. Pharmaceutical valuable compounds of the following general formula:

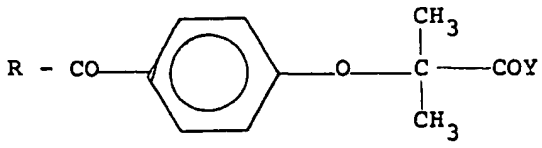
(I) wherein

A is selected from the group consisting of $C(CH_3)_2$ and a phenyl substituted alkyl chain having from 1 to 4 C;

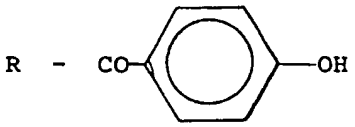
R is selected from H, free or W-halogenated CH_3, C_2H_5 and C_3H_7 groups and C_6H_5; and

Y is selected from OH, lower alkoxy having 1 to 3 C, aliphatic amines selected from the group consisting of dimethyl-, diethyl-, and ethylamino-ethylamine, and heterocyclic amines selected from the group consisting of piperidine, 2-methyl piperidine, 4-methyl piperidine, morpholine, pyrrolidine, piperazine, N-phenyl-, N-methyl, N-p-methoxyphenyl-, N-p-chlorophenyl-piperazine and hexamethyl-eneimime, when prepared according to the process of claim 1 or its obvious chemical equivalent.

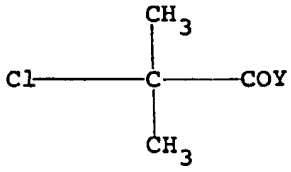
6. Process for preparing compounds having useful pharmaceutical properties of the general formula



wherein R is selected from the group consisting of H, CH_3, C_2H_5, C_3H_7 and C_6H_5 and Y is selected from the group consisting of OH, OCH_3, OC_2H_5, and OC_3H_7 comprising reacting a compound of the formula

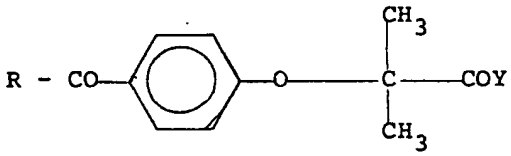


with a compound of the formula



wherein R and Y are as above defined, in the presence of a basic condensing agent.

7. Pharmaceutically valuable compounds of the general formula



wherein R and Y are as defined in claim 6, when prepared according to the process of claim 6 or its obvious chemical equivalent.